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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,026	CROOKE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ~~June 16, 2004~~ June 17, 2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence search alignments*.

DETAILED ACTION

Pursuant to Applicants Appeal Brief filed August 25, 2004, and the Examiner's reconsideration of the claims, prosecution is reopened on the instant application. The Examiner has reconsidered the claims in light of a new method of searching oligonucleotide sequences performed at the Patent and Trademark Office. This new method of searching was not available during the previous prosecution of the instant application. Any new art now cited was uncovered using this new searching method.

Response to Amendment

Applicants Appeal Brief filed August 25, 2004 is acknowledged.

First off, it is noted that the Appeal Brief filed August 25, 2004 addresses an outstanding issue regarding the consideration of the Information Disclosure Statement dated March 31, 2003 and refiled on June 18, 2004. Documents AQ and BQ have been considered by the Examiner since an English translation of the Japanese Abstract has been provided.

Second, Applicants argue the outstanding 35 U.S.C. 103(a) rejection against claims 1, 4-10, 12 and 13 as being unpatentable over Cases et al. [WO 99/67368] in view of Bennett et al. [U.S. Patent No. 6,613,567] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288). It is noted that Applicants arguments regarding this rejection will be addressed as they relate to the new 35 U.S.C. 103(a) rejection made of record below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-10, 12, and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "said compound" in line 5. There is insufficient antecedent basis for this limitation in the claim because the claim makes reference to an antisense oligonucleotide. Claims 4-10, 12, and 13 are dependent on claim 1 and are thus included in this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-10, 12, and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a written description rejection.**

The instant claims are drawn to an antisense oligonucleotide 8 to 50 nucleobases in length targeted to a coding region of a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3), wherein said compound specifically hybridizes with said region and inhibits the expression of human acyl CoA cholesterol acyltransferase-2 by at least 40%.

The instant specification teaches a single coding region o a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3) (see Table 1). Given their broadest reasonable interpretation, the instant claims are drawn to an antisense oligonucleotide 8 to 50 nucleobases in length targeted to **a** coding region of a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3), which could necessarily imply multiple coding regions. Applicants have not described multiple coding regions of a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3). The application as filed only teaches a single coding region of a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3). Replacement with the language, an antisense oligonucleotide 8 to 50 nucleobases in length targeted to **the** coding region of a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3), wherein said compound specifically hybridizes with said region and inhibits the expression of human acyl CoA cholesterol acyltransferase-2 by at least 40% would overcome the instant rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Cases et al. [U.S. Patent No. 6,579,974].

Claim 1 is drawn to an antisense oligonucleotide 8 to 50 nucleobases in length targeted to a coding region of a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3), wherein said compound specifically hybridizes with said region and inhibits the expression of human acyl CoA cholesterol acyltransferase-2 by at least 40%. Claim 12 is dependent on claim 1 and include all the limitations of claim 1 with the further limitation comprising an antisense oligonucletoide of claim 1 and a pharmaceutically acceptable carrier or diluent.

Cases et al. disclose an ACAT-2 antisense primer with the following sequence 5'-GGTCCACATCAGCACGTTCC-3' (see SEQ ID NO:8). This antisense primer is reverse

complementary to bases 1418-1437 of SEQ ID NO:3 of the instant invention. It is noted that the reverse complimentarity between the antisense primer disclosed by Cases et al. and nucleobases 1418-1437 of SEQ ID NO:3 is contiguous and exhibits 100% local similarity to nucleobases 1418-1437 of SEQ ID NO:3 of the instant invention (see attached sequence alignment). Given this high degree of similarity, the antisense primer disclosed by Cases et al. meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" with a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 as defined in the instant specification at pages 9 and 10, lines 31-35 and 1-3, respectively. Accordingly, the antisense primer disclosed by Cases et al. would specifically hybridize to bases 1418-1437 of SEQ ID NO:3 as claimed. It is noted that the instant claim recites an antisense oligonucleotide comprising a pharmaceutically acceptable carrier. Since Cases et al. disclose that the antisense primer was used as in a PCR reaction, and one skilled in the art would readily accept that a PCR reaction is conducted in a solution containing water and/or a buffer, it is understood that either water or a buffer constitute as a pharmaceutically acceptable carrier.

The burden of establishing whether the prior art oligonucleotide primer has the further function of inhibiting gene expression by at least 40% under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15

USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the antisense primer disclosed by Cases et al. would or would not have the additional functional limitation of "inhibiting expression" of human acyl CoA cholesterol acyltransferase-2 gene by at least 40% under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1 and 12 are anticipated by Cases et al.

Claims 1, 4-10, 12, and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Cowsert et al. [U.S. Patent No. 6,482,644].

Claims 1 and 12 are described above. Claims 4-10 and 13 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations, wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; and wherein the antisense oligonucleotide is a chimeric oligonucleotide.

Cowsert et al. disclose a modified antisense oligonucleotide targeted to human Dual specific phosphatase 8 with the following sequence: 5'-tggtcatagaccaccacgtc-3' (see SEQ ID NO:17). This antisense oligonucleotide is reverse complementary to bases 1184-1200 of SEQ ID NO:3 of the instant invention. It is noted that the reverse complimentarity between the antisense oligonucleotide targeted to human Dual specific phosphatase 8 disclosed by Cowsert et al. and nucleobases 1184-1200 of SEQ ID NO:3 is not contiguous. However, the antisense oligonucleotide targeted to human Dual specific phosphatase 8 disclosed by Cowsert et al. exhibits 94% local similarity to nucleobases 1184-1200 of SEQ ID NO:3 of the instant invention, as it contains only one mismatch (see attached sequence alignment). Given this high degree of similarity, the antisense oligonucleotide targeted to human Dual specific phosphatase 8 disclosed by Cowsert et al. meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" since the instant specification at pages 9 and 10, lines 31-35 and 1-3, respectively teaches, "it is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable." Accordingly, the antisense oligonucleotide disclosed by Cowsert et al. would specifically hybridize to bases 1184-1200 of SEQ ID NO:3 as claimed.

The burden of establishing whether the prior art antisense oligonucleotide has the further function of inhibiting gene expression by at least 40% under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a

sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the antisense oligonucleotide disclosed by Cowsert et al. would or would not have the additional functional limitation of "inhibiting expression" of human acyl CoA cholesterol acyltransferase-2 gene by at least 40% under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1, 4-10, 12, and 13 are anticipated by Cowsert et al.

Claims 1, 4-10, 12, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Dean et al. [U.S. Patent No. 6,180,353].

Dean et al. disclose a modified antisense oligonucleotide targeted to human daxx with the following sequence: 5'-ctgcagaggccagaaacaca-3' (see SEQ ID NO:109). This antisense oligonucleotide is reverse complementary to bases 1275-1294 of SEQ ID NO:3 of the instant invention. It is noted that the reverse complimentarity between the antisense oligonucleotide targeted to human daxx disclosed by Dean et al. and nucleobases 1275-1294 of SEQ ID NO:3 is

not contiguous. However, the antisense oligonucleotide targeted to human daxx disclosed by Dean et al. exhibits 85% local similarity to nucleobases 1275-1294 of SEQ ID NO:3 of the instant invention, as it contains three mismatches (see attached sequence alignment). Given this high degree of similarity, the antisense oligonucleotide targeted to human daxx disclosed by Dean et al. meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" since the instant specification at pages 9 and 10, lines 31-35 and 1-3, respectively teaches, "it is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable." Accordingly, the antisense oligonucleotide disclosed by Dean et al. would specifically hybridize to bases 1275-1294 of SEQ ID NO:3 as claimed.

The burden of establishing whether the prior art antisense oligonucleotide has the further function of inhibiting gene expression by at least 40% under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently

possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the antisense oligonucleotide disclosed by Dean et al. would or would not have the additional functional limitation of "inhibiting expression" of human acyl CoA cholesterol acyltransferase-2 gene by at least 40% under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1, 4-10, 12, and 13 are anticipated by Dean et al.

Claims 1, 4-10, 12, and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Zhang et al. [U.S. Patent No. 6,503,754].

Zhang et al. disclose a modified antisense oligonucleotide targeted to human BH3 interacting domain death agonist with the following sequence: 5'-cacagtccatggcctgggca -3' (see SEQ ID NO:22). This antisense oligonucleotide is reverse complementary to bases 903-922 of SEQ ID NO:3 of the instant invention. It is noted that the reverse complimentarity between the antisense oligonucleotide targeted to human BH3 interacting domain death agonist disclosed by Zhang et al. and nucleobases 903-922 of SEQ ID NO:3 is not contiguous. However, the antisense oligonucleotide targeted to human BH3 interacting domain death agonist disclosed by Zhang et al. exhibits 85% local similarity to nucleobases 903-922 of SEQ ID NO:3 of the instant invention, as it contains three mismatches (see attached sequence alignment). Given this high degree of similarity, the antisense oligonucleotide targeted to human BH3 interacting domain death agonist disclosed by Zhang et al. meets the structural limitations of the claimed invention

and would be expected to "specifically hybridize" since the instant specification at pages 9 and 10, lines 31-35 and 1-3, respectively teaches, "it is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable." Accordingly, the antisense oligonucleotide disclosed by Zhang et al. would specifically hybridize to bases 903-922 of SEQ ID NO:3 as claimed.

The burden of establishing whether the prior art antisense oligonucleotide has the further function of inhibiting gene expression by at least 40% under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the antisense oligonucleotide disclosed by Zhang et al. would or would not have the additional functional

limitation of "inhibiting expression" of human acyl CoA cholesterol acyltransferase-2 gene by at least 40% under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1, 4-10, 12, and 13 are anticipated by Zhang et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-10, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oelkers et al. (Journal of Biological Chemistry, 1998 Vol. 273:26765-26771) [Applicants IDS reference BA, submitted November 19, 2002] in view of Chong et al. (Drugs, 2000 Vol. 60:55-93) [Applicants IDS reference AL, submitted November 19, 2002], and Bennett et al. [U.S. Patent No. 6,613,567].

Claim 1 is drawn to an antisense oligonucleotide 8 to 50 nucleobases in length targeted to a coding region of a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3), wherein said compound specifically hybridizes with said

region and inhibits the expression of human acyl CoA cholesterol acyltransferase-2 by at least 40%. Claims 4-10 and 13 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations, wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; and wherein the antisense oligonucleotide is a chimeric oligonucleotide. Claim 12 is dependent on claim 1 and include all the limitations of claim 1 with the further limitation comprising an antisense oligonucletoide of claim 1 and a pharmaceutically acceptable carrier or diluent.

Oelkers et al. teaches the full-length sequence of human acyl CoA cholesterol acyltransferase-2 as represented in SEQ ID NO:3 of the instant invention (see Oelkers et al. Figure 2). Oelkers et al. do not teach antisense targeted to human acyl CoA cholesterol acyltransferase-2 including antisense with a length of 8 to 50 nucleobases. Oelkers et al. also do not teach antisense targeted to a nucleic acid encoding human acyl CoA cholesterol acyltransferase-2 wherein the antisense comprises modified internucleoside linkages or wherein the antisense is a chimeric antisense molecule.

Chong et al. teach acyl CoA cholesterol acyltransferase (ACAT) inhibitors prevent or treat atherosclerosis by controlling cholesterol metabolism. Chong et al. also teach there are ongoing clinical studies with small molecule ACAT inhibitors, but preliminary reports suggest

poor gastrointestinal tract tolerability in humans, however the development of water-soluble ACAT inhibitors may solve this problem (see page 73, first column).

Bennett et al. teach antisense oligonucleotides that can specifically hybridize with different regions in a target gene, including the coding region (see column 3, lines 57-67 and column 4, lines 1-62 and Tables 1 and 2). Bennett et al. further teach a wide range of antisense oligonucleotides that inhibit gene expression at various inhibition capacities, including inhibition by at least 40% (see Tables 1 and 2). Bennett et al. further teach antisense oligonucleotides with modified nucleobases, such as 2'-O-methoxyethyl modified amidites, wherein at least one 2'-O-methoxyethyl modification is in a cytidine; and in which every 2'-O-methoxyethyl modified cytidine is a 5-methyl cytidine (see column 16, lines 64-67, and column 18, lines 30-44). Bennett et al. finally teach antisense oligonucleotides as chimeric oligonucleotides comprising 2'methoxyethyl wings and a deoxy gap (see column 28, lines 51-59 and Tables 3 and 4). Bennett et al. teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases.

It would have been *prima facie* obvious to one of ordinary skill in the art to design an inhibitor to acyl CoA cholesterol acyltransferase-2 using the motivation of Chong et al. to control cholesterol metabolism. It would have been obvious to one of ordinary skill in the art to make antisense nucleic acids, 8 to 50 nucleobases in length, targeted to the coding region of acyl CoA cholesterol acyltransferase-2, since Oelkers et al. teaches the full-length sequence of human acyl CoA cholesterol acyltransferase-2 as represented in SEQ ID NO:3 of the instant invention and since Bennett et al. explicitly taught the design of antisense oligonucleotides, 20 nucleobases

in length, that can specifically hybridize with the coding sequence of a gene of interest. It would have been obvious to modify the antisense oligonucleotide with such modifications including phosphorothioate modified backbones or 2'-O-methoxyethyl sugar moieties, for example, since Bennett et al. taught that such modifications increase nucleic acid stability in the presence of nucleases. One of ordinary skill in the art would have expected success in making an antisense oligonucleotide targeted to the coding region of a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3), wherein said compound specifically hybridizes with said region and inhibits the expression of human acyl CoA cholesterol acyltransferase-2 by at least 40%, since Bennett et al. demonstrate that following generic teachings of making antisense oligonucleotides to a target, it would be expected that oligonucleotides will inhibit by at least 40%, since a wide range of oligonucleotides of various capacities are created and inhibit gene expression to various degrees, including by at least 40% (see Bennett et al. Tables 1 and 2)

One of ordinary skill in the art would have been motivated to design an inhibitor of human acyl CoA cholesterol acyltransferase-2 since the prior art taught ACAT inhibitors to prevent or treat atherosclerosis by controlling cholesterol metabolism. One of ordinary skill in the art would have been motivated to make antisense oligonucleotide inhibitors targeted to a coding region of a nucleic acid molecule encoding human acyl CoA cholesterol acyltransferase-2 since the Chong et al. taught the development of water-soluble ACAT inhibitors may correct for poor gastrointestinal tract tolerability in humans, and Bennett et al. taught oligonucleotides are designed to modulate gene expression for antisense attack of specific genes. One of ordinary skill in the art would be motivated to make such antisense oligonucleotides of a length within the

range of 8 to 50 nucleotides for ease of synthesis and delivery to cells in culture, and because it is conventional in the art to make antisense within this size range (as exemplified by Bennett et al.). One of ordinary skill in the art would have been motivated to modify the antisense oligonucleotide since Bennett et al. taught modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases

Therefore the invention as a whole would have been obvious to one of ordinary skill in the art.

Response to Arguments

It is noted that in the Office Action mailed May 1, 2003, claims 1, 4-10, 12 and 13 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cases et al. [WO 99/67368] in view of Bennett et al. [U.S. Patent No. 6,613,567] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

In response to this rejection, Applicants argue that the combination of Cases, Bennett and Fritz does not teach or suggest Appellants' invention. Specifically, Applicants argue that Cases in combination with Bennett and Fritz does not provide a reasonable expectation of success which is required to render the present invention obvious. Applicants contend that Bennett and Fritz are cited for "generic" teachings related to antisense compounds, but neither is directed to antisense oligonucleotides to ACAT-2. Applicants argue that Cases provides the coding sequence of the human ACAT-2 gene as SEQ ID NO:2, however, and as admitted to by the Examiner, SEQ ID NO:2 of Cases is not identical to SEQ ID NO:3 of Appellants' invention, as it

is missing approximately 60 nucleotides of the coding sequence of human ACAT-2. Second, Applicants argue that the Examiner acknowledges that Cases does not discuss a compound targeted to a coding region of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 that hybridizes with and inhibits expression of human acyl CoA cholesterol acyltransferase by at least 40% or such antisense oligonucleotides modified as specified by the present dependent claims.

The Examiner finds the first argument persuasive. In light of this argument, the Examiner has made a new 35 USC 103(a) rejection and included the disclosure of Oelkers et al. (Journal of Biological Chemistry, 1998 Vol. 273:26765-26771) who teaches the full-length sequence of human acyl CoA cholesterol acyltransferase-2 as represented in SEQ ID NO:3 of the instant invention (see Oelkers et al. Figure 2). The Examiner finds the second argument persuasive (in part). First, Applicant argues against the references individually, but must consider the rejection based upon the combination of the references. *See*, MPEP 2145. Second, and in light of Applicants argument, the Examiner has made a new reconstructed 35 USC 103(a) rejection against claims 1, 4-10, 12, and 13 as being unpatentable over Oelkers et al. (Journal of Biological Chemistry, 1998 Vol. 273:26765-26771) in view of Chong et al. (Drugs, 2000 Vol. 60:55-93), and Bennett et al. [U.S. Patent No. 6,613,567]. The combination of the references of the newly reconstructed 35 USC 103(a) rejection renders the instant invention obvious as discussed beginning at page 11 above.

Applicants argue that there is no way for anyone of skill in the art to predict whether one may obtain any particular percentage of inhibition simply by prior knowledge of generic antisense technology. Appellants argue that there is nothing in this combination of prior art that

suggests such success and one of skill might be motivated to "hope for" such a level of success using generic technology, however, nothing in the prior art allows for such an expectation. Applicants make reference to the fact that Appellants' assignee, which is a company that specializes antisense technology and uses the latest in bioinformatics programs, have demonstrated repeatedly that one may investigate 80 or more oligonucleotides in attempts to identify a target site permitting inhibition at a specific high level for a specific gene. Applicants argue that one cannot anticipate similar results when one looks at completely different genes.

This argument is not found persuasive by the Examiner because a brief review of the first randomly chosen 10 patents issued to the assignee that published before Applicants filing date (i.e. 6,001,992, 6,124,133, 6,136,603, 6,140,124, 5,985,558, 6,020,199, 6,046,049, 6,133,032, and 6,140,126) reveals that each and every patent contains anywhere from a few to many oligonucleotides that inhibit target gene expression by at least 40%. Thus, one skilled in the art would readily achieve at least 40% inhibition in the expression of any particular gene under generally some assay conditions.

Applicants further argue with regard to these combined references suggesting that antisense sequences to ACAT-2 are desirable, is simply a suggestion that it may be obvious to try. Applicants contend that there must be some reasons, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. Applicants argue that an obviousness rejection cannot be made by combining documents to make the suggestion that it is "obvious to try" to make antisense compounds to target ACAT-2, simply because others have made antisense compounds to other unrelated proteins and that antisense sequences to ACAT-2 would be desirable, if made.

The Examiner has found this argument persuasive (in part). First, Applicant argues against the references individually, but must consider the rejection based upon the combination of the references. *See*, MPEP 2145. Second, and in light of Applicant's argument, the Examiner has provided a specific reference which provides motivation to make antisense compounds to target ACAT-2. For example, Chong et al. taught that acyl CoA cholesterol acyltransferase (ACAT) inhibitors prevent or treat atherosclerosis by controlling cholesterol metabolism. Chong et al. also teach there are ongoing clinical studies with small molecule ACAT inhibitors, but preliminary reports suggest poor gastrointestinal tract tolerability in humans (see page 73, first column). Chong et al. further teach the development of water-soluble ACAT inhibitors may solve this problem. Therefore, Chong et al. provide clear motivation to make antisense compounds to target ACAT-2 to prevent or treat atherosclerosis by controlling cholesterol metabolism and since antisense compounds are water-soluble, one of skill in the art would be motivated to make antisense compounds to target ACAT-2 to correct for poor gastrointestinal tract tolerability in humans.

In summary, Appellants believe that the Examiner continues to improperly use hindsight to construct the outstanding obviousness rejection, and has failed to interpret the prior art as a whole, from the point of view of a person having ordinary skill in the art at the time the invention was made, as required by 35 USC 103. Reversal of the outstanding rejection of pending claims 1, 4-10, and 13 under 35 USC 5 103(a) has respectfully requested.

Applicant's arguments and request have been fully considered and are found persuasive (in part). First, Applicant argues against the references individually, but must consider the rejection based upon the combination of the references. *See*, MPEP 2145. Second, and in light

of Applicants arguments, the Examiner has reconstructed a new 35 USC 103(a) rejection with the teachings of Oelkers et al. who teaches the full-length sequence of human acyl CoA cholesterol acyltransferase-2 as represented in SEQ ID NO:3 of the instant invention (see Oelkers et al. Figure 2). Chong et al. was relied upon to provide motivation to make an inhibitor to human acyl CoA cholesterol acyltransferase-2. Chong et al. further provide motivation to make an antisense compound inhibitor to human acyl CoA cholesterol acyltransferase-2 since water-soluble ACAT inhibitors may correct for poor gastrointestinal tract tolerability. Bennett et al. taught antisense oligonucleotides that can specifically hybridize with different regions in a target gene, and a wide range of antisense oligonucleotides that inhibit gene expression at various inhibition capacities, including inhibition by at least 40%, which provides an expectation of success. Therefore, in light of the new 35 USC 103(a) rejection as presented above, the combination of references renders the instant invention obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
November 10, 2004

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Applicants Copy
Sequence Search alignment ...

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RESULT 39
AR255958/c
LOCUS       AR255958                 20 bp    DNA     linear   PAT 20-DEC-2002
DEFINITION  Sequence 17 from patent US 6482644.
ACCESSION   AR255958
VERSION     AR255958.1  GI:27305217
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 20)
  AUTHORS   Cowsert,L.M.
  TITLE     Antisense modulation of dual specific phosphatase 8 expression
  JOURNAL   Patent: US 6482644-A 17 19-NOV-2002;
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Applicants Copy
Sequence Search alignment...

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ACCESSION   AR126680
VERSION     AR126680.1  GI:14113273
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 20)
  AUTHORS   Dean,N.M. and Cowsert,L.M.
  TITLE     Antisense modulation of daxx expression
  JOURNAL   Patent: US 6180353-A 109 30-JAN-2001;
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Db         20 TGTGTTTCTGGCCTCTGCAG 1
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Applicants Copy

Sequence search alignment...

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DEFINITION  Sequence 8 from patent US 6579974.
ACCESSION   AR344231
VERSION     AR344231.1  GI:33740140
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 20)
  AUTHORS   Cases,S., Farese,R.V. Jr. and Erickson,S.K.
  TITLE     Acyl CoA:cholesterol acyltransferase (ACAT-2)
  JOURNAL   Patent: US 6579974-A 8 17-JUN-2003;
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VERSION     AR271778.1  GI:29703346
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SOURCE      Unknown.
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REFERENCE   1  (bases 1 to 20)
  AUTHORS   Zhang,H. and Wyatt,J.
  TITLE     Antisense modulation of BH3 interacting domain death agonist
            expression
  JOURNAL   Patent: US 6503754-A 22 07-JAN-2003;
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Applicants Copy
Sequence Search alignment...